National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

Process Validation (PV)

World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
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General Considerations Before Submitting PV Data

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General Considerations Before Submitting PV Data

Topics of the Session

1) Checklist
2) Q & A of ASEAN Guideline On Process Validation
3) Case study/ Common Problems

General Considerations Before Submitting PV Data

Checklist

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Generic Medicine Section,
Product Registration Center

Checklist

No	Title	Requirements	Remark/ Justification
A	Summary	Overview of the process of validation study	
B	Introduction	- Objective & Reason of study - Frequency of study - Marketing Country - Location of study	Basic information

Checklist

C	**Batches used for Validation**	- **Batch number** - **Manufacturing date** - **Batch Size(**)** *** Commercial OR Pilot** **- Validated Batch Formulation**	• **The validation lot size should be the same as intended standard commercial scale lot.** • **At least, three(3) batches for option 1** • **Validated formulation must be the same as the proposed formulation**

Checklist

D	**Manufacturing equipment**	**- Equipment list with information such as** **- ID number/model/class** **- Calibration & Qualification status**	**All equipments must be fully validated and calibrated.**

Checklist

E	**Critical process Steps**	- **Short description of manufacturing process** - **Schematic drawing; or Flow Chart** - **Holding time** **Non Sterile (example)** - **Dispensing, Mixing, granulation, drying, blending, compression, coating, etc.** **Sterile (example)** - **Sterilization & Depyrogenation of containers, closures, equipments and component, aseptic process simulation (media fill), terminal sterilization, filtration, etc.**	**Validated manufacturing process should be consistent with the proposed manufacturing process.**

Checklist

and parameters	**Example:** - **Speed, time & duration, temperature & etc.** - **worst case scenario**	**This information is important to ensure that only critical parameters & validated process variables were used during manufacturing.** **The study should be robust enough to prove that those ranges of variables were able to produce proposed specification.** **For Media Fills** **There is a requirement to compare the parameters used for production filling and for media fills.**

Checklist

F	**Acceptance Criteria**	**Data comparison against acceptable reference & against proposed acceptance criteria** - **Reference pharmacopeia** - **CoA & Stability Study**	
G	**Sampling Plan**	**Where, when, how, & how many?** - **Sample quantity/amount,** - **Location & Point of sampling** - **Method of sampling** - **Equipment Diagram** - **Time,** - **Frequency** - **'worst case' Scenario**	

Checklist

H	**Tabulation of test results**	**Data presentation:** - **Table and Charts**	
I	**Batch Analysis**	**Summary of the results on:** - **Critical process parameters.** - **In process control** - **Finished product specification**	
J	**Evaluation of data, including statistical process control analysis.**	**Data analysis** - **Statistical analysis** - **Process capability index**	

Checklist

K	**Evaluation of data including comparison against acceptance criteria**	**Data analysis and its assessment against PV acceptance criteria**	
L	**Discussions on deviations and out of specification results**	**Summary and action on any ;** - **Failed results,** - **Deviations** - **Out of specification** - **Corrective Action & Preventive Action (CAPA)**	

Checklist

M	Conclusion and recommendations	Final outcome. Re-validation condition.	

Checklist

Please take note that

This checklist is a brief outline of the requirements. Nevertheless, NPCB reserves the right to request for more information when the information is deemed critical or when further clarification is needed.

General Considerations Before Submitting PV Data

Q & A of ASEAN Guideline on Process Validation

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Q & A of ASEAN Guideline on Process Validation

1. Does this guideline also apply to biological/biotechnological products?

This guideline applies to the manufacturing process of the finished product for New Chemical Entities and Generic Drug Applications. The general principles mentioned in the guidelines also apply to biotechnological and biological products. However, more extensive data may be required.

Q & A of ASEAN Guideline on Process Validation

2. For Option 2, should data related to Development Pharmaceutics be also submitted for generic products?

The ASEAN Common Technical Requirement (ACTR) states that Pharmaceutical Development is not required for the Generic Drug Applications. However, if the applicant is not able to submit under option 1 and chooses option 2 under the ASEAN Guideline on Process Validation, the applicant is required to submit the Pharmaceutical Development information as well as validation report on one pilot batch and validation scheme.

Q & A of ASEAN Guideline on Process Validation

3. For option 3, in the absence of pre-approval dossiers pertaining to process validation, would concurrent validation be acceptable?

(Note: 'pre-approval dossiers' refer to the set of documents including process validation documents that were used in the submission to a reference country for drug registration application.)
As stipulated in the Guideline, under certain circumstances where validation documents may not form part of the pre-approval dossiers, the DRA may request for Validation Report or Validation Scheme. In addition, the applicant is required to undertake that 3 consecutive full production batches are successfully validated before the product is marketed and to submit the report to DRA upon request. If any approach other than prospective validation is proposed such as concurrent validation, justification should be provided and prior consent from the DRA should be obtained before the submission of the drug registration application.

Q & A of ASEAN Guideline on Process Validation

4. (1)Are orphan drugs subjected to the full registration requirements? (2)Using the concurrent approach, does it mean the product can be released for sale immediately after meeting quality requirements?

Unless otherwise specified by the DRA of the individual Member Countries, orphan drugs are subject to full registration requirements. If the concurrent approach is used, prior consent is required from the DRA.

Q & A of ASEAN Guideline on Process Validation

5. Can Concurrent Validation be used for infrequently manufactured products?

Concurrent validation can be used for infrequently manufactured products; however the applicant should seek prior consent from the DRA before submitting the application for drug product registration.

Q & A of ASEAN Guideline on Process Validation

6. If the validation data submitted for 3 consecutive production batches showed that they fully comply with specifications but do not fulfill the process validation acceptance criteria, would they be approved for marketing?

The onus is on the manufacturer to ensure that the manufacturing process is well controlled prior to manufacturing the batches for marketing. The manufacturer should provide justification for not meeting the acceptance criteria of process validation and may need to re-validate the process before releasing the said product batches which meet the quality specification for sale.

Q & A of ASEAN Guideline on Process Validation

7. What is the acceptable range permitted for critical process parameters?

A nominal or target value for the critical process parameter with an allowable normal operating range should be defined and justified. There are no fixed formulae for this. The range is established based on scientific data available, process robustness and the expected impact of the critical process parameter on critical quality attributes defined in product specification.

Q & A of ASEAN Guideline on Process Validation

8. Can bracketing /matrixing approach be adopted for process validation?

This approach is not recommended unless it can be justified.

Q & A of ASEAN Guideline on Process Validation

9. Should IQ and OQ data be submitted in the process validation study report?

Installation Qualification IQ, Operational Qualification OQ and Performance Qualification PQ data are not required for submission. However, IQ, OQ and PQ should be performed satisfactorily as a prerequisite to validation studies. Complete data report should be made available for site inspection by relevant regulatory authorities.

Q & A of ASEAN Guideline on Process Validation

10. Should homogeneity data be submitted together with the validation report?

Homogeneity and blend uniformity data must be included in the validation protocol where homogeneity is a critical quality attribute.

Q & A of ASEAN Guideline on Process Validation

11. What is an acceptable validation lot size?

The validation lot size should be the same size as an intended standard commercial scale lot. If a range in lot size is proposed for commercial process, the variation in lot size should be demonstrated not to adversely impact the quality characteristics of the finished product.

Q & A of ASEAN Guideline on Process Validation

12. Should validation batches be placed on stability program?

It is not a requirement but it would be good practice to place at least 1 concurrent validation batch or 3 prospective batches on stability program. This provides efficient use of resources as well as fulfills the commitment to submit stability data on 3 full scale batches.

Q & A of ASEAN Guideline on Process Validation

13. When can we submit the result of 3 consecutive full production batches if the results are not available at the point of application and either option 2 or option 3 is chosen?

If option 2 or option 3 is chosen, process validation of 3 consecutive full production batches can be performed post-registration, subject to concurrence by the DRA. The report should then be submitted after approval of the product but prior to launching / marketing of the product. However, if the product has been marketed in other country / countries, the DRA may request for the validation data of 3 production batches during the registration process.

Q & A of ASEAN Guideline on Process Validation

14. What is the acceptable limit for Cpk?

The guideline states that a Cpk of 1.0, 1.33 and 2.0 represents a 3, 4, 6 sigma respectively. The general rule of thumb is, for a good process under statistical control, Cpk value should be greater than 1.33. If a Cpk value of a process is less than 1.33, the applicant should seek advice from DRA for acceptability.

Q & A of ASEAN Guideline on Process Validation

15. For legacy products which have been historically manufactured at a site, can retrospective validation be used to support process validation?

Retrospective validation may be performed to support process validation for existing **non-sterile** products which are already on the market for some time.
In addition, the following conditions should be met:
– No change in formulation.
– No change in manufacturing process or analytical method.
– No change in equipment or site(s) of manufacturing.
– CpK ≥ 1.33 (If a Cpk < 1.33, the applicant should seek advice from DRA for acceptability) based on 10-20 consecutive batches.

Q & A of ASEAN Guideline on Process Validation

16. For certain product, premix/pellets/direct compression granules are used in the manufacturing process of the finished product. Should process validation data for the premix/pellets/direct compression granules be submitted together with the process validation data of the product?

The manufacturing process of premix/pellets/direct compression granules must be controlled and validated if the properties of the premix/pellets/direct compression granules have a direct impact on the finished product. Therefore, process validation documents for premix/pellets/direct compression granules should be submitted.

General Considerations Before Submitting PV Data

Case Study/ Common Problems

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Case Study/ Common Problems

Scenario 1

Validated batch size is different from the proposed batch size in section B1.1 (Batch Manufacturing Formula) and section B1.2 (Attachment of Batch Formula Document).

Case Study/ Common Problems

Example

- PV option 1 is chosen
- Commercial batch size proposed in section B1.1 & B1.2 is 300,000 tablets.
- Validated batch size in the PV study is 100,000 tablets.

Please take note that

The validation lot size should be the same size as an intended standard commercial scale lot.

(Q & A of ASEAN Guideline on Process Validation)

Case Study/ Common Problems

Scenario 2

Documents submitted for sterile products in section P3.4 (Process Validation and/or Evaluation) are not adequate.

Case Study/ Common Problems

Example

Aseptically filled products

or

Terminally sterilised products

Only PV study was submitted in section P3.4 (Process Validation and/or Evaluation).

Case Study/ Common Problems

Please take note that

Basic documents* required for an aseptically filled products including, but not limited to:

a) Media fill study,

b) Validation data of the sterilization & depyrogenation of containers, closure, equipments and components,

c) Filtration validation study,

d) PV study

Case Study/ Common Problems

Basic documents* required for a terminally sterilised products including, but not limited to:

a) Validation data of the sterilization & depyrogenation of containers, closure, equipments and components,

b) Validation data of the terminal sterilizer/ other terminal sterilization process

c) PV study

* the information in the studies have to fulfill the requirements which stated in the ASEAN guideline.

Case Study/ Common Problems

Scenario 3

Discrepancy of the information in sections P3.2(Manufacturing Process and Process Control), P3.2.1 (Manufacturing Process Flowchart) & P3.4 (Process Validation and/or Evaluation) regarding the

(a) Sterilization method used

(b) Manufacturing process parameters.

Case Study/ Common Problems

Example for (a) -sterilization method used

No terminal sterilization process stated in sections P3.2 (Manufacturing Process and Process Control)& P3.2.1 (Manufacturing Process Flowchart), but terminal sterilization process was stated in the PV study.-confusing

Case Study/ Common Problems

Example for (b) - manufacturing process parameters

In section P3.2, blending time is stated 20 minutes.

In PV study, blending time challenged is 25 minutes.

Case Study/ Common Problems

Scenario 4

Process validation study of the premix is not submitted.

Case Study/ Common Problems

Example

In section product validation (STEP 1), premix is declared. However, only PV study of the finished product is found in section P3.4 (Process Validation and/or Evaluation).

9. Contain Premix : YES

List of premix:- :

No.	Premix form	Manufacturer Name	Manufacturer Address	GMP Certificate	Formulation Process	Manufacturing Process	Specification of Analysis	Certification of Analysis
1	API PREMIX	A	B	C	D	E	F	G

Case Study/ Common Problems

Please take note that

The manufacturing process of premix/pellets/direct compression granules must be controlled and validated if the properties of the premix/pellets/direct compression granules have a direct impact on the finished product.

(Q & A of ASEAN Guideline on Process Validation)

Case Study/ Common Problems

Scenario 5

Amendment made in the PV documents without signature or history of changes.

Case Study/ Common Problems

Please take note that

- It is important to comply with the basic requirements of the GMP for Documentation.
- Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information.
- Where appropriate, the reason for the alteration should be recorded.

(PIC/S GMP GUIDE (PART I: BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS; PE 009-11 (Part I))

Case Study/ Common Problems

Scenario 6

Documents submitted are not relevant to the product which is intended to be registered.

Case Study/ Common Problems

Example

1) Validation data of the product which was conducted at another manufacturing site was submitted.
2) The information of the sterilizer/tunnel/oven used to sterilize/depyrogenate the components/primary packaging of the product which stated in the validation report or qualification report are different from the information which stated in the PV report. (eg. different ID no. of the equipments)

Case Study/ Common Problems

Example

3) Submitted media fill batches are not simulating the normal production fill situation and **no justification or explanation was submitted**. (eg. different vial size filled in the media fill study compared to the proposed vial size of the product)

Thank You!